Co-Morbidities in Dravet Syndrome

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Disclosures

Zogenix
   Research funding
   Consulting

West Pharmaceuticals
   Research Funding

Pediatric Epilepsy Research Foundation
   Research Funding

Greenwich pharmaceuticals
   DSMB

Colorado Department of Public Health and Environment
   Research Funding

There are no conflicts relevant to today’s talk
Objectives

Review and update several comorbidities

Gait
Sleep
GI issues
Autonomic symptoms
Cognition
Behavior
Themes I Hear In Clinic

- Constipation provokes seizures
- Poor sleep
- Long duration to eat
- Ambulation concerns
- No response to pain
  - Leads to unexpected injuries

- Autonomic symptoms
  - Flushing, not tolerating heat/cold
  - Racing or slow HR
  - Changes in skin pigmentation

- Behavior
  - Perseveration
  - Safety
Dravet Syndrome Evolution

Gautallina and Dulac, 2017
Limited, but improving!
Gait

Crouched gait
  No children under 6 years
  ½ Of children 6-12 yr
  8/9 of children > 13yr

Crouched gait is associated with mobility issues

Mild Parkinsonian symptoms in 11/12 adults
  Bradykinesia
  Rigidity
  Cogwheeling

Does not appear to be related to seizure medication use

Rodd, 2012
Rilestone, 2012
Fasano, 2014
Aljaafari et al, 2017
EMG and Nerve conduction

- 12 patients
  - 2-17 years old
  - Reflexes decrease in 4 of 12
- All had gait abnormalities on exam
- Nerve conduction
  - Normal
- EMG (study of the muscle)
  - Evidence of "chronic denervation"
  - 7 with definite Motor neuropathy
  - 3 with probable motor neuropathy

Gitiaux et al, 2016
Colorado Experience EMG/NCV

17 children tested
  2-21 years
All with gait abnormalities
9 with abnormal testing
  5 with NCV abnormalities
  8 with EMG abnormalities

Suggests primary demyelinating or primary axonal changes, seen in motor nerves, sensory nerves, or in both.

Dubow et al, AES 2018
## Endocrine Abnormalities

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Subjects with an abnormal result / Total # tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1</td>
<td>6 / 14</td>
</tr>
<tr>
<td>TSH</td>
<td>2 / 23</td>
</tr>
<tr>
<td>Sex hormones</td>
<td></td>
</tr>
<tr>
<td>FSH</td>
<td>2 / 6</td>
</tr>
<tr>
<td>LH</td>
<td>1 / 6</td>
</tr>
<tr>
<td>Estradiol</td>
<td>0 / 1</td>
</tr>
<tr>
<td>Testosterone</td>
<td>3 / 10</td>
</tr>
<tr>
<td>Cortisol</td>
<td>2 / 8</td>
</tr>
</tbody>
</table>

Eschbach et al, 2017
Endocrine Abnormalities

2 children with IGF-1 abnormalities had additional testing to confirm growth hormone deficiency.

One child had complete pituitary dysfunction:
- thyroid problems
- cortisol problems

Two children treated with testosterone

Eschbach et al, 2017
Weight Compared To Norms

Predicted Mean*

95% Confidence Interval

Individual's Percentile

*Predicted mean and CI are calculated by transforming predicted Z-scores from a mixed linear regression model with a random intercept and slope.

Eschbach et al, 2017
Height Compared To Norms

*Predicted mean and CI are calculated by transforming predicted Z-scores from a mixed linear regression model with a random intercept and slope.

Eschbach et al, 2017
Height and Weight

• Over time height and weight fall below the expected average for the US population

• Height falls off before weight

• With poor nutrition – weight falls off before height – what we are seeing is not nutrition

• So why does this happen?
  ▪ Genetics
  ▪ Endocrine dysfunction
  ▪ Medications

Eschbach et al, 2017
Sleep

- Sleep study
  - 6 children
  - no abnormalities!!!
    
    Dhamija, 2014

- Parental Concerns
  - Reported in 97%
  - Little change with age
    
    Villas et al, 2017

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### Parent Reported Sleep Concerns*

<table>
<thead>
<tr>
<th>Sleep Issues</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any sleep problem</td>
<td>147 (82%)</td>
</tr>
<tr>
<td>Apnea</td>
<td>55 (31%)</td>
</tr>
<tr>
<td>Difficulty falling asleep</td>
<td>116 (65%)</td>
</tr>
<tr>
<td>Awakens from sleep</td>
<td>123 (69%)</td>
</tr>
<tr>
<td>Short time of sleep</td>
<td>95 (53%)</td>
</tr>
</tbody>
</table>

* One hundred seventy-nine respondents for this section of the survey.

Knupp et al, 2017
Sleep

- 43 of 57 with sleep problems
- 6 of 16 had abnormalities with home oximetry testing

Licheni et al, 2017
GI Issues

- Appetite concerns 68%
- Small stature, underweight 39%

Villas et al, 2017

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Parental Perception of Gastrointestinal and Feeding Concerns

<table>
<thead>
<tr>
<th>Feeding Issues</th>
<th>N (%)</th>
<th>% Poor Appetite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor appetite</td>
<td>65 (36%)</td>
<td>—</td>
</tr>
<tr>
<td>Decreased variety of food</td>
<td>88 (50%)</td>
<td>59%</td>
</tr>
<tr>
<td>Prolonged meal times</td>
<td>118 (68%)</td>
<td>48%</td>
</tr>
<tr>
<td>Assistance with feeding</td>
<td>59 (34%)</td>
<td>57%</td>
</tr>
<tr>
<td>Difficulty swallowing</td>
<td>50 (29%)</td>
<td>46%</td>
</tr>
<tr>
<td>Difficulty chewing</td>
<td>72 (41%)</td>
<td>43%</td>
</tr>
<tr>
<td>Food fads</td>
<td>118 (68%)</td>
<td>45%</td>
</tr>
<tr>
<td>Picky eater</td>
<td>115 (66%)</td>
<td>48%</td>
</tr>
</tbody>
</table>

Knupp et al, 2017
# Autonomic Symptoms

<table>
<thead>
<tr>
<th>Other reported symptoms</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooping causes seizures</td>
<td>179</td>
<td>21.2%</td>
</tr>
<tr>
<td>Unable to tolerate cold</td>
<td>179</td>
<td>55.3%</td>
</tr>
<tr>
<td>Hands turn blue</td>
<td>179</td>
<td>36.3%</td>
</tr>
<tr>
<td>Frequent falls</td>
<td>179</td>
<td>70.4%</td>
</tr>
<tr>
<td>Avoid stairs</td>
<td>179</td>
<td>33.5%</td>
</tr>
<tr>
<td>Balance problems with change of surfaces</td>
<td>179</td>
<td>75.4%</td>
</tr>
<tr>
<td>Little response to pain</td>
<td>179</td>
<td>76.0%</td>
</tr>
<tr>
<td>Doesn’t report injuries</td>
<td>169</td>
<td>61.0%</td>
</tr>
<tr>
<td>Frequent illness</td>
<td>179</td>
<td>69.8%</td>
</tr>
<tr>
<td>Prefers to play with adults</td>
<td>169</td>
<td>65.1%</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>169</td>
<td>24.9%</td>
</tr>
<tr>
<td>Short stature</td>
<td>169</td>
<td>36.7%</td>
</tr>
<tr>
<td>Lighter skin</td>
<td>169</td>
<td>34.3%</td>
</tr>
</tbody>
</table>

Knupp et al, 2017
Autonomic Symptoms

- Bradycardia – 13%
- Tachycardia – 30%
- Temperature dysregulation - 80%

Villas et al, 2017
Cognition decreases over time
No correlation found between
  Age at seizure onset
  Status epilepticus
  Number of seizures
  Myoclonus or absence seizures

Greater cognitive decline was associated with:
  Longer duration of contra-indicated medications in the first year of life
  Earlier diagnosis of developmental delay
  Age at first afebrile seizure

Parents report worsening of cognition with prolonged seizures or increase in seizure frequency

De lange et al, 2018
Villas et al, 2017
Behavior

Attention problems
Impulsiveness
Perseverative responses
Deficits in planning

• Parent report
  ▪ Impulsive 38%
  ▪ ADD/ADHD 39%

• Parent survey
  ▪ Attention 69%
  ▪ Perseveration 49%
  ▪ Oppositional behavior 35%
  ▪ PDD 25%
  ▪ Anxiety 15%

Villas et al, 2017
Knupp et al, 2017
CAREGIVER BURDEN
Time And Difficulty Of Tasks
## Impact On Work Productivity And Leisure Time

<table>
<thead>
<tr>
<th></th>
<th>EQ-5D VAS ≥65 (n=18)</th>
<th>EQ-5D VAS &lt;65 (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td><strong>Weekly time missed from work</strong> (hours)</td>
<td>7.4 (15.2)</td>
<td>0.5 (0.0, 2.8)</td>
</tr>
<tr>
<td><strong>Weekly time missed from leisure</strong> (hours)</td>
<td>31.0 (53.9)</td>
<td>7.0 (1.8, 23.0)</td>
</tr>
<tr>
<td><strong>Effect caregiving had on work productivity</strong></td>
<td>39.1 (25.6)</td>
<td>52.0 (13.8, 58.0)</td>
</tr>
<tr>
<td><strong>Effect caregiving had on leisure time</strong></td>
<td>55.1 (24.0)</td>
<td>55.5 (39.5, 69.3)</td>
</tr>
</tbody>
</table>

*SD, standard deviation; VAS, visual analog scale; WPAI, Work Productivity and Activity Impairment.*
### Per-Person Direct Cost of Care

<table>
<thead>
<tr>
<th>Cost Component</th>
<th>Mean Unit Cost</th>
<th>Caregiver-Reported Annualized Rate Mean (SD)</th>
<th>Annual Cost Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional Healthcare Utilization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-Home Visits</td>
<td>$214^{11}$</td>
<td>46.23 (137.64)</td>
<td>$9,894 ($29,456)</td>
</tr>
<tr>
<td>Doctor Visits</td>
<td>$245^{11}$</td>
<td>11.13 (9.07)</td>
<td>$2,728 ($2,221)</td>
</tr>
<tr>
<td>Emergency Department Visits</td>
<td>$788^{11}$</td>
<td>1.90 (2.27)</td>
<td>$1,497 ($1,789)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>$10,204^{11}$</td>
<td>1.13 (2.16)</td>
<td>$11,565 ($22,001)</td>
</tr>
<tr>
<td>Ground Ambulance</td>
<td>$1,111^{17}$</td>
<td>0.67 (1.58)</td>
<td>$741 ($1,753)</td>
</tr>
<tr>
<td>Air Ambulance</td>
<td>$7,160^{17}$</td>
<td>0.07 (0.25)</td>
<td>$477 ($1,786)</td>
</tr>
<tr>
<td><strong>Complementary and Alternative Healthcare Utilization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiropractic Services</td>
<td>$36^{11}$</td>
<td>6.53 (16.80)</td>
<td>$235 ($605)</td>
</tr>
<tr>
<td>Multivitamin Use</td>
<td>$10</td>
<td>6.33 (9.07)</td>
<td>$63 ($91)</td>
</tr>
<tr>
<td>Essential Oil Use</td>
<td>$10</td>
<td>2.57 (5.90)</td>
<td>$26 ($59)</td>
</tr>
<tr>
<td>Marijuana Prescription</td>
<td>$150^{18}</td>
<td>0.33 (0.83)</td>
<td>$50 ($125)</td>
</tr>
<tr>
<td><strong>Total Annual Direct Cost Mean (95% interval)</strong></td>
<td>$27,276</td>
<td></td>
<td>($15,757, $41,294)</td>
</tr>
</tbody>
</table>
# Indirect Cost Burden

<table>
<thead>
<tr>
<th>Lost Productivity (n=24, 73%)*</th>
<th>Caregiver-Reported Time Mean (SD)</th>
<th>Annual Cost* Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absenteeism</td>
<td>381 (704) hours</td>
<td>$7,587 ($16,941)</td>
</tr>
<tr>
<td>Presenteeism</td>
<td>616 (719) hours</td>
<td>$12,338 ($19,196)</td>
</tr>
<tr>
<td>Lost Leisure Time (n=33, 100%)*</td>
<td>2,047 (2,929) hours</td>
<td>$52,415 ($74,932)</td>
</tr>
<tr>
<td>Income Loss due to Caregiving (n=21, 64%)</td>
<td></td>
<td>$9,242 ($19,410)</td>
</tr>
<tr>
<td><strong>Total Annual Indirect Cost</strong></td>
<td></td>
<td><strong>$81,582 ($57,253, $110,151)</strong></td>
</tr>
</tbody>
</table>

Total time commitment = 380 eight hour work days/ year
Caregiver Burden

Caregivers spend significant amount of time providing care for children with Dravet syndrome

Direct and indirect cost of care is great

Total time commitment = 380 eight hour work days per year!
Multi-Disciplinary Care

- Physical therapy and rehabilitation medicine evaluation
- Levodopa trial
- Parkinsonism
- Cognition and Behavior
  - Early intervention referral
  - Individualized education plan
  - Evaluate for ADHD
  - Behavioral therapy
- Gait Abnormalities
- Sleep Disturbances
- Sleep specialist, if needed
- Endocrine
- Appetite and Feeding
  - Consider the following:
    - Swallow evaluation
    - Dietician assessment
    - Gastroenterology referral
- Seizures
  - Maintenance anti-seizure medication
  - Appropriate seizure action plan
  - Epilepsy evaluation
Putting It All Together

• Dravet Syndrome is more than seizures and delay in cognition
• Many of these associated symptoms likely affect quality of life and many may require multi-disciplinary care
• Making progress in identifying and characterizing these issues, now need more research to identify best management in these areas